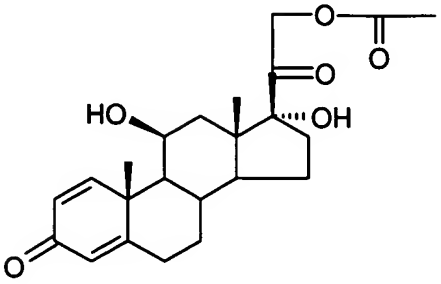
Pfizer CentreSource

Prednisolone Acetate USP
Prednisolone Acetate USP Micronized



$C_{23}H_{30}O_6$ MW 402.49

NOMENCLATURE

Pregna-1,4-diene-3,20-dione, 21-(acetyloxy)-11,17-dihydroxy-, (11β)-
11β,17,21-Trihydroxypregna-1,4-diene-3,20-dione 21-acetate
11β,17-Dihydroxy-3,20-dioxopregna-1,4-dien-21-yl acetate
CAS *52-21-1*
Glucocorticoid
Laboratory Code: PNU-5955
USAN, BAN, JAN: Prednisolone Acetate

DESCRIPTION

Prednisolone Acetate from Pfizer is a white to practically white, odorless, crystalline powder. It melts at about 235°C, with some decomposition. It is practically insoluble in water; slightly soluble in acetone, in alcohol, and in chloroform.

USP SPECIFICATIONS

Test	Specification
Identification	
A. Infrared	Positive
B. Ultraviolet	Positive
Absorptivity Difference Dried Basis	Not More Than 2.5%
Specific Rotation (Dried Basis)	+112° to +119° (dioxane)
Loss on Drying	Not More Than 1.0%
Chromatographic Purity	
Any Individual Impurity	Not More Than 1.0%
Total Impurities	Not More Than 2.0%
Color in Solution	Not More Than 0.05
Assay (Dried Basis)	97.0% to 102.0%

In addition to the US Registration Specifications, the following apply to Prednisolone Acetate from Pfizer labeled "EP".

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CHARACTERS

Prednisolone Acetate from Pfizer is a white or almost white, crystalline powder. It is practically insoluble in water; slightly soluble in alcohol and in methylene chloride. It melts at about 230°C, with decomposition.

EP SPECIFICATIONS

Test	Specification
Identification	
A. Infrared	Positive
Specific Optical Rotation (Dried Basis)	+112° to +119° (dioxane)
Related Substances	Meets Test
Any Individual Impurity	Not More Than 1.0%
Not More Than One Individual Impurity	Not More Than 0.5%
Total Impurities	Not More Than 2.0%
Loss on Drying	Not More Than 0.5%
Assay (Dried Basis)	97.0% to 103.0%

Additional Tests & Particle Size for Micronized Grades

Parameter	Target	Method
Particle Size Average	Not More Than 15 microns	Celloscope
Particle Size Std. Dev.	Report Results	Celloscope

Regulatory Filings:

See Prednisolone acetate under Regulatory

Organic Volatile Impurities

Of the solvents targeted in USP 26 General Chapter <467>, only methylene chloride may appear in bulk pharmaceutical products manufactured by Pfizer at the Kalamazoo plant. For those products where OVI testing is required, our material will meet the compendial limits for methylene chloride and other solvents that may be added to the target list in the future.

No OVI requirement exists in the USP 26 monograph for Prednisolone Acetate, but Prednisolone Acetate from Pfizer meets the requirements of USP 26 General Chapter <467>.

ICH Residual Solvents

As of 01 July 2000, Pfizer's laboratories began to internally report all solvents that are present above the assay detection limit. During the review of the batch data, it is verified that no solvents are present above the ICH limits. Therefore, all lots of Prednisolone Acetate released after 01 July 2000 will meet the ICH residual solvent guidance.

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Solvent	Pfizer Specification *	ICH Class and Specification
Residual Solvents (Total)	Not More Than 0.5%	
Acetone	No individual specification	3: Not More Than 0.5%
Methylene Chloride	Not More Than 100 ppm	2: Not More Than 600 ppm

* Pfizer does not have Registered Specifications for residual solvents, only quality control Targets.

Other solvents used: *t*-butyl alcohol, ethyl acetate, methanol

ICH Residual Metals

Pfizer is currently developing a strategy to assess the detection and quantitation of ICH residual metals in Pfizer's active pharmaceutical ingredients. Currently, the only residual metal known to be present in Prednisolone Acetate from Pfizer is Osmium, with a quality control Target of NMT 10 ppm.

TSE Certificate of Suitability

Certificate No. R0-CEP 2000-271-Rev 00 was granted to Pfizer by the European Directorate for the Quality of Medicines on 24 October 2001 for five years, for the product Prednisolone Acetate. A copy of the certificate is available upon request.

Viral Safety Statement for Active Pharmaceutical Ingredients (APIs)

Pfizer has reviewed the viral safety risks of its manufacturing practices for production of non-biological active pharmaceutical ingredients (APIs). The API Prednisolone Acetate presents no viral safety concerns. Pfizer APIs produced by bacterial or fungal fermentation and/or bioconversion processes are not considered to present viral safety risks. The raw materials used in the stages of production are sterilized prior to inoculation with a monoculture of the desired microorganisms. Only Pfizer's bioconversion reactions that employ purified enzymes (e.g. introduction of a double bond at the 1,2-position of the steroid ring system) use animal-derived materials that are not sterilized prior to introduction to the process. To support the safety of these enzymes, suppliers are required to provide documentation to Pfizer that these materials are in compliance with the CPMP and CVMP guidances on minimization of the risk of transmitting animal spongiform encephalopathy (TSE) agents via medicinal or veterinary products. Pfizer requires suppliers to provide similar certification for all TSE-risk animal-derived materials.

Statement Regarding Genetically Modified Materials in the Production of Active Pharmaceutical Ingredients (APIs)

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The organism(s) currently used in the fermentation/bioconversion of plant sterols to produce intermediates that are chemically transformed into Prednisolone Acetate are not genetically engineered. However, Pfizer does not make any commitment that would preclude using genetically modified (recombinant) strains at some future date.

There are a number of ingredients used in the fermentation/bioconversion process that are derived from plants that are major agricultural products in the United States. It is well known that the U.S. agriculture industry has a growing reliance upon genetically modified (recombinant) plants such as corn and soybeans. Although some grain handlers and processors have contacted farmers about needing to segregate genetically modified seeds from non-genetically modified seeds, this concept has only recently been introduced and lacks effective enforcement and monitoring components. Pfizer has not evaluated the sources of ingredients for fermentation/bioconversion-derived intermediates and APIs relative to ingredients having been derived in part from genetically engineered varieties of plants or other organisms.

Vegetable Origin of Raw Materials

Pfizer produces steroid active pharmaceutical ingredients (APIs) by what is best described as a semi-synthetic process using a crude mixture of vegetable sterols that are isolated from various oilseeds as the starting material. These vegetable sterols, stigmasterol and sitosterol, are processed through several fermentation and chemical steps to yield Prednisolone Acetate.

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Gluten

The raw materials used in the manufacture of Prednisolone Acetate are not derived from the gluten-containing grains wheat, rye, barley, or oats. Therefore, although Pfizer does not specifically assay for the presence of gluten, it is unlikely that any gluten proteins are present.

Polymorphism

Evaluation of infrared (IR) spectra and x-ray diffraction (XRD) patterns indicate that Prednisolone Acetate from Pfizer has only one crystal structure (or crystal form). IR and XRD assays have been implemented to assure detection of any occurrence of undesired polymorphs.

Chirality

Prednisolone Acetate has seven chiral carbons: C8, C9, C10, C11, C13, C14, and C17. Pfizer's manufacturing process can modify the chirality of three of them: C9, C11, and C17.

Stereoisomer Content

Please note that none of the known impurities of Prednisolone Acetate are stereoisomers of Prednisolone Acetate. Therefore, the stereoisomer content is LT 0.1%.

Commercial Availability Of API And Impurities Standards

Prednisolone (PNU-5962, PNU-199999, SC-8189, E-208)
EP Impurity B

EP (www.pheur.org), catalog # P2700000, 200 mg, €79
USP (www.usp.org), catalog # 1555005, 200 mg, $150
Steraloids (www.steraloids.com), catalog # P0650-000, 100 mg, $5 (other sizes available) (called "1, 4-PREGNADIEN-11β, 17, 21-TRIOL-3, 20-DIONE")
Research Plus (www.researchplus.com), catalog # 3010-16, 1 g and 5 g sizes (called "1,4-PREGNADIEN-11b,17a,21-TRIOL-3,20-DIONE")
Sigma, 4 catalog entries

Hydrocortisone Acetate (PNU-2476)
EP Impurity A

EP (www.pheur.org), catalog # H1400000, 100 mg, €79
USP (www.usp.org), catalog # 1317007, 200 mg, $150
Steraloids (www.steraloids.com), catalog # Q3883-000, 100 mg, $8.50 (other sizes available) (called "4-PREGNEN-11β, 17, 21-TRIOL-3, 20-DIONE 21-ACETATE")
Research Plus (www.researchplus.com), catalog # 3313-16, 1 g and 5 g sizes (called "4-PREGNEN-11b,17a,21-TRIOL-3,20-DIONE 21-ACETATE")
Sigma, 5 catalog entries (called "Hydrocortisone 21-acetate")